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CLINICAL THERAPEUTICS

Outpatient Fluoroquinolone Prescription Fills in the United States, 2014 to 2020: Assessing the Impact of Food and Drug Administration Safety Warnings

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ABSTRACT The impact of United States Food and Drug Administration (FDA) safety warnings on outpatient fluoroquinolone use is unclear. Annual changes in outpatient ciprofloxacin, levofloxacin, and moxifloxacin prescription fills (IQVIA National Prescription Audit databases) were assessed using a regression model. Monthly fills during baseline (August 2014 to April 2016) and first (May 2016 to June 2018) and second FDA warning periods (July 2018 to February 2020) were compared by interrupted time series analysis. From 2015 through 2019, total fluoroquinolone fills decreased from 35,616,786 (111.1/1,000 persons) to 21,100,050 (64.3/1,000 persons) annually (10.8% annually [$P = 0.001$]). Ciprofloxacin, levofloxacin, and moxifloxacin fills decreased annually by 10.4% ($P = 0.001$), 11.2% ($P < 0.001$), and 17.7% ($P = 0.008$), respectively. During the baseline period, there was no significant change in monthly fluoroquinolone fills. In May 2016 and during the first warning period, monthly fluoroquinolone fills decreased significantly ($P < 0.001$); the trend of decreased fills was significantly greater than that of the baseline period ($P = 0.02$). There was no change in fluoroquinolone fills in July 2018. Monthly fills decreased significantly throughout the second warning period ($P < 0.001$), but the trend did not differ from that of the first warning period. Trends for ciprofloxacin, the most commonly prescribed fluoroquinolone, were similar to those for the class. Fills of prescriptions by infectious diseases specialists ($P < 0.005$) and nurse practitioners ($P = 0.04$) significantly increased during the study. U.S. outpatient fluoroquinolone prescription fills significantly decreased from August 2014 to February 2020, most strongly in association with May 2016 FDA warnings. FDA safety warnings are useful tools for leveraging outpatient antimicrobial stewardship.

KEYWORDS FDA, Food and Drug Administration, fluoroquinolone, outpatient

Fluoroquinolones were first approved by the United States (U.S.) Food and Drug Administration (FDA) in 1980. The class has enjoyed extensive use due to favorable properties such as high oral bioavailability, widespread distribution and tissue penetration, relatively broad spectra of activity, and infrequent dosing schedules. Fluoroquinolone prescriptions in the U.S. increased from 1991 through 2010 before plateauing from 2011 through 2015 (1). Over 70% of U.S. fluoroquinolone expenditures are in community pharmacies (2). It is estimated that 25% of outpatient fluoroquinolone prescriptions are for indications that do not require antibiotics or for which a fluoroquinolone is not first-line therapy (3). The Centers for Disease Control and Prevention (CDC) published *Core Elements of Outpatient Antibiotic Stewardship* in 2016, which called for action to improve antibiotic prescribing, tracking, and reporting of utilization and education about appropriate use (4). Efforts at outpatient fluoroquinolone stewardship have yielded mixed results. Multifaceted strategies have achieved reductions in overall and inappropriate fluoroquinolone use in

Citation Buehrle DJ, Wagener MM, Clancy CJ. 2021. Outpatient fluoroquinolone prescription fills in the United States, 2014 to 2020: assessing the impact of Food and Drug Administration safety warnings. Antimicrob Agents Chemother 65:e00151-21. https://doi.org/10.1128/AAC.00151-21.

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Received 27 January 2021
Returned for modification 23 March 2021
Accepted 12 April 2021
Accepted manuscript posted online 19 April 2021
Published 17 June 2021

TABLE 1 Dates of FDA warnings about fluoroquinolones

Date	Intervention
8 July 2008	FDA mandate that a boxed warning be added to fluoroquinolone product labeling warning of increased risk of tendinitis and tendon rupture
30 March 2011	FDA mandate adding information about exacerbations of myasthenia gravis to the boxed warning
15 August 2013	FDA issues drug safety communication regarding risk for possibly permanent nerve damage from fluoroquinolones. FDA also mandates that drug labeling be updated to better describe the serious side effect of peripheral neuropathy.
12 May 2016	FDA issue drug safety communication advising that serious adverse events associated with fluoroquinolone use generally outweigh their benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections. Fluoroquinolones are recommended to be reserved for patients without alternative options. These disabling and potentially permanent adverse events were effects on the tendons, muscles, joints, nerves, and central nervous system.
26 July 2016	FDA mandate revising boxed warning to include information appearing in the May 2016 drug safety communication.
10 July 2018	FDA issues drug safety communication that strengthened the warnings in the prescribing information of fluoroquinolones regarding adverse events on blood glucose levels and mental health.
20 December 2018	FDA issue drug safety communication regarding the risk of aortic dissection and aortic aneurysm rupture associated with fluoroquinolone use.

some, but not all, health care systems (5–7). In many instances, reductions were not sustained in the absence of ongoing interventions (6, 8).

Antibiotics are the second leading cause of emergency department (ED) visits due to adverse drug events (ADEs) in the U.S., behind only anticoagulants (9). Fluoroquinolones are the class of antibiotics most likely to cause an ADE requiring hospital admission (9). Several fluoroquinolones have been withdrawn from the market by the FDA due to ADEs. Beginning in 2008, the FDA has issued a series of safety warnings about the class (Table 1). The impact of these announcements on fluoroquinolone prescribing in the U.S. is unclear. A study of 29 southeastern U.S. hospitals found that 2016 warnings were associated with a significant decrease in inpatient fluoroquinolone use through 2017 (10). A public health care system in Texas that added 2016 FDA warnings to orders for oral fluoroquinolones as part of a multifaceted stewardship intervention documented reductions in outpatient utilization through 2018 (5). However, a single-center cohort study of outpatient family medicine practices found that 2016 warnings were not associated with immediate decreases in fluoroquinolone use (11). To date, no studies have directly addressed associations between FDA warnings and nationwide outpatient fluoroquinolone prescriptions in the U.S. However, the absence of evidence for decreased fluoroquinolone utilization nationally through 2015 (1) suggests that earlier FDA warnings did not have a significant impact on prescribing practices.

The objectives of this study were to characterize fluoroquinolone prescription fills by outpatient pharmacies in the U.S. from 2014 (when data became available from IQVIA National Prescription Audit [NPA] databases) through February 2020 and to assess the potential impact of FDA safety warnings on prescription fills.

RESULTS

Fluoroquinolone prescriptions filled per year. In 2015, 35,616,786 fluoroquinolone prescriptions were filled in the United States, which equated to 111.1 prescriptions per 1,000 persons. In 2019, 21,100,050 prescriptions were filled (64.3 prescriptions per 1,000 persons). From 2015 through 2019, fluoroquinolone prescription fills decreased annually by 10.8% (decrease of 11.9 prescriptions per 1,000 persons per year (95% confidence interval [CI], −9.5 to −14.3; $P = 0.001$) (Table 2).

Ciprofloxacin was the most commonly filled fluoroquinolone, with 21,691,363 (67.7 prescriptions per 1,000 persons) and 13,265,679 (40.4 prescriptions per 1,000 persons) fills in 2015 and 2019, respectively. Levofloxacin fills in 2015 and 2019 were 13,351,190 (41.6 prescriptions per 1,000 persons) and 7,635,154 (23.3 prescriptions per 1,000 persons), respectively. Moxifloxacin fills were 574,233 (1.8 prescriptions per 1,000 persons) and 199,217 (0.6 prescriptions per 1,000 persons), respectively. Prescription fills of

TABLE 2 Change in fluoroquinolone prescribing by agent and clinician specialty, 2015 through 2019

Variable	Annual change in no. of prescription fills per 1,000 persons	95% confidence interval (%)	*P* value
Total fluoroquinolones, all providers	−12.0	−14.3 to −9.6	0.001
Ciprofloxacin, all providers	−7.0	−8.6 to −5.4	0.001
Levofloxacin, all providers	−4.7	−5.4 to −4.0	<0.001
Moxifloxacin, all providers	−0.3	−0.4 to −0.1	0.008
Total fluoroquinolone prescriptions by clinician specialty			
Family and general practice	−2.9	−3.5 to −2.4	<0.001
Internal medicine	−0.2	−0.3 to −0.1	0.006
Nurse practitioner	0.06	0.01 to 0.12	0.041
Osteopathic medicine	−0.07	−0.12 to −0.02	0.016
Physician assistant	−0.002	−0.04 to 0.03	0.88
Urology	−0.03	−0.04 to −0.01	0.019
Emergency medicine	−0.02	−0.04 to −0.01	0.019
Obstetrics and gynecology	−0.02	−0.02 to −0.01	0.003
General surgery	−0.03	−0.03 to −0.02	0.001
Geriatrics	−0.01	−0.01 to −0.006	0.003
Oncology	−0.003	−0.007 to −0.001	0.04
Otolaryngology	−0.02	−0.01 to −0.01	0.001
Pediatrics	−0.006	−0.008 to −0.003	0.007
Podiatry	−0.002	−0.004 to −0.001	0.015
Dentistry	−0.002	−0.003 to 0.001	0.06
Nephrology	0.0002	−0.002 to 0.002	0.74
Internal medicine/pediatrics	−0.005	−0.007 to −0.002	0.009
Infectious diseases	0.003	0.002 to 0.005	0.005
Unspecified specialty	−0.03	−0.05 to −0.02	0.004
Other medical subspecialty	0.02	−0.04 to −0.01	0.014
Other surgical subspecialty	−0.001	−0.007 to −0.001	0.046
Other	−0.014	−0.02 to −0.01	0.007

ciprofloxacin, levofloxacin, and moxifloxacin decreased annually by 10.4% (−7 prescriptions/1,000 persons [95% CI, −5.4 to −8.6; $P = 0.001$]), 11.2% (−4.7 prescriptions/1,000 persons [95% CI, −4.0 to −5.4; $P < 0.001$]), and 17.7% (−0.3 prescriptions/1,000 persons [95% CI, −0.15 to −0.4; $P = 0.008$]), respectively (Table 2). In comparison, there was no significant change in amoxicillin fills from 2015 through 2019 (55,664,885 prescription fills (175 prescriptions per 1,000 persons) in 2015 and 54,968,618 prescription fills (172.8 prescriptions per 1,000 persons) in 2019.

Fluoroquinolone prescription fills before and after FDA warnings. During the baseline period (August 2014 to April 2016), there was no significant reduction in monthly fluoroquinolone prescription fills (Table 3; Fig. 1). In the first month of the first warning period (May 2016), there was a significant decrease in fluoroquinolone prescription fills (−1.2 prescriptions per 1,000 persons [95% CI, −1.8 to −0.6; $P < 0.001$]). Thereafter, monthly prescription fills of fluoroquinolones decreased significantly throughout the first warning period (May 2016 to June 2018) (−0.07 prescriptions per 1,000 persons per month [95% CI, −0.09 to −0.05; $P < 0.001$]); the trend of decreasing monthly fluoroquinolone prescription fills during this period was significantly greater than the trend during the baseline period (relative change, −0.06 prescriptions per 1,000 persons per month [95% CI, −0.11 to −0.01; $P = 0.02$]).

There was no change in monthly fluoroquinolone prescription fills in July 2018, the first month of the second warning period. Monthly prescription fills decreased significantly throughout the second warning period (July 2018 to February 2020) (−0.05 prescriptions per 1,000 persons per month [95% CI, −0.07 to −0.03; $P < 0.001$]), but the trend did not differ significantly from that of the first warning period.

Ciprofloxacin, levofloxacin, and moxifloxacin prescription fills before and after FDA warnings. Ciprofloxacin prescription fill trends during baseline and first warning and second warning periods were similar to those observed for fluoroquinolones overall (Table 3; Fig. 1). Like ciprofloxacin, levofloxacin fills did not change significantly

TABLE 3 Outpatient fluoroquinolone prescription fills in the United States, August 2014 through February 2020[h]

	Estimated monthly prescription fills,[a] base level[b]		Monthly trend in prescription fills,[a] baseline period			Change in prescription fills,[a] May 2016[c]			Monthly trend in prescription fills,[a] first warning period		
Agent	No. of prescriptions	95% CI	Monthly trend (no. of prescriptions)	95% CI	*P* value	Change (no. of prescriptions)[a]	95% CI	*P* value	Monthly trend (no. of prescriptions)	95% CI	*P* value
FQ total[g]	9.6	8.9, 10.4	−0.01	−0.06, 0.36	0.63	**−1.2**	**−1.8, −0.61**	**<0.001**	**−0.07**	**−0.09, −0.05**	**<0.001**
CIP	5.8	5.5, 6.1	−0.02	−0.03, 0.01	0.06	**−0.39**	**−0.63, −0.16**	**0.001**	**−0.05**	**−0.06, −0.05**	**<0.001**
LVX	3.7	3.0, 4.3	0.01	−0.03, 0.05	0.63	**−0.79**	**−1.33, −0.24**	**0.006**	−0.02	−0.04, 0.01	0.10
MXF	0.2	0.16, 0.23	**−0.01**	**−0.005, −0.001**	**0.009**	**−0.02**	**−0.05, −0.001**	**0.038**	**−0.001**	**−0.002, −0.001**	**0.001**
AMX	15.2	13.1, 17.2	0.09	−0.05, 0.22	0.22	−1.62	−3.94, 0.71	0.17	0.019	−0.10, 0.13	0.72

[a]Presented as prescription fills per 1,000 persons, using U.S. Census monthly estimates of the national population.
[b]Estimated number of prescription fills per 1,000 persons at start baseline period.
[c]Change in prescription fills from April 2016 to May 2016, based on values from predicted trends for each drug (Fig. 1).
[d]Change in trend for May 2016 to June 2018, relative to August 2014 to April 2016.
[e]Change in prescription fills from June 2018 to July 2018, based on values from predicted trends for each drug (Fig. 1).
[f]Change in trend for July 2018 to February 2020, relative to May 2016 to June 2018.
[g]Total prescriptions of ciprofloxacin, levofloxacin, and moxifloxacin.
[h]Data were analyzed by interrupted time series regression model using Newey-West standard errors (STATA 16.1). Significant results appear as bolded text. Baseline period, August 2014 through April 2016. First warning period, May 2016 through June 2018. Second warning period, July 2018 through February 2020. FQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, amoxicillin; CI, confidence interval.

TABLE 3 (Continued)

Relative change in trend of monthly prescription fills,[a] first warning period[d]			Change in prescription fills,[a] July 2018[e]			Monthly trend in prescription fills,[a] second warning period			Relative change in trend of monthly prescription fills,[a] second warning period[f]		
Monthly trend (no. of prescriptions)	95% CI	*P* value	Change (no. of prescriptions)[a]	95% CI	*P* value	Monthly trend (no. of prescriptions)	95% CI	*P* value	Monthly trend (no. of prescriptions)	95% CI	*P* value
−0.06	**−0.11, −0.01**	**0.02**	−0.13	−0.55, 0.30	0.57	**−0.05**	**−0.07, 0.03**	**0.001**	0.025	−0.001, 0.06	0.12
−0.04	**−0.06, −0.02**	**0.001**	0.16	−0.06, 0.38	0.14	**−0.04**	**−0.05, −0.03**	**<0.001**	0.015	−0.01, 0.03	0.09
−0.03	−0.07, 0.02	0.21	−0.28	−0.72, 0.17	0.21	−0.001	−0.03, 0.01	0.37	0.01	−0.02, 0.04	0.55
0.002	−0.001, 0.004	0.18	−0.004	−0.016, 0.009	0.55	−0.001	−0.001, 0.001	0.27	**0.001**	**0.001, 0.002**	**0.019**
−0.06	−0.23, 0.11	0.45	−1.42	−3.83, 0.99	0.24	0.10	−0.04, 0.25	0.16	0.08	−0.09, 0.26	0.35

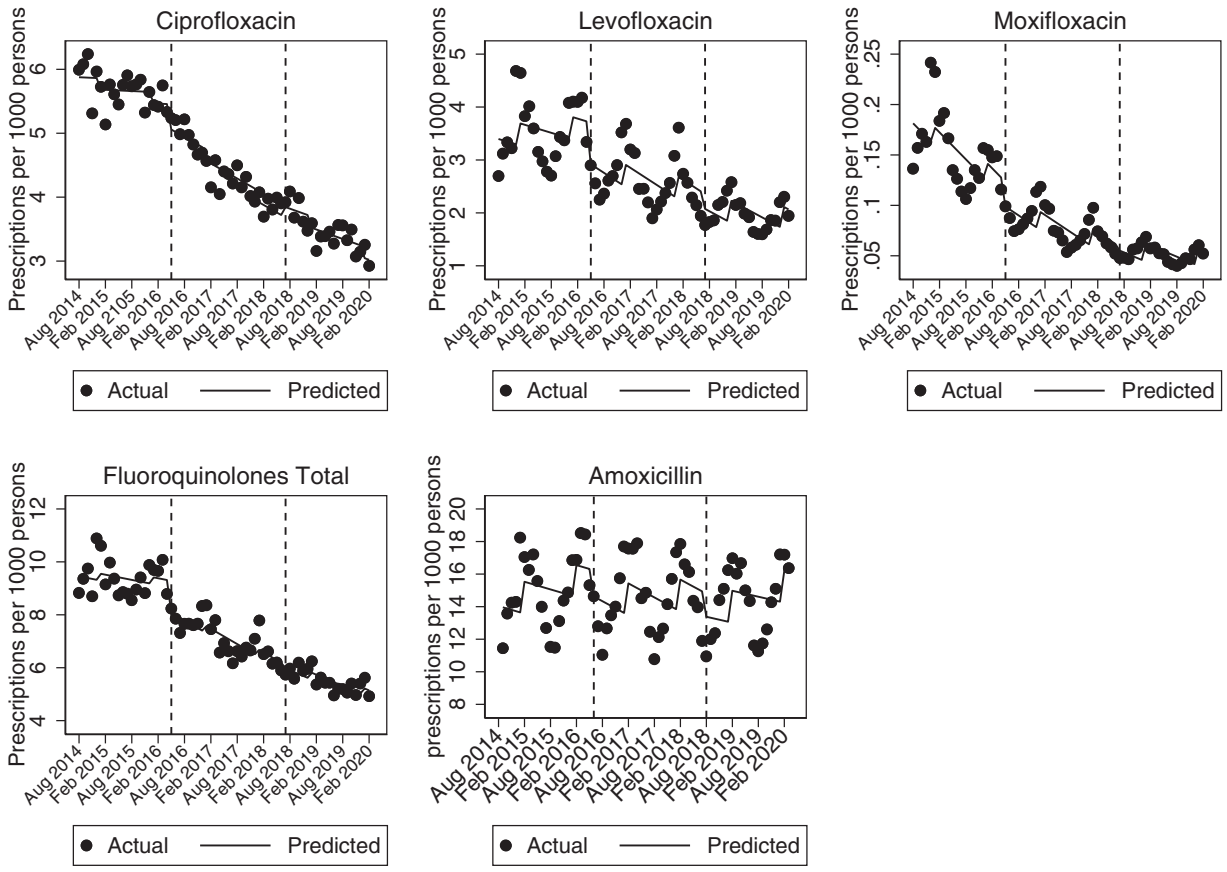

FIG 1 Trends in outpatient fluoroquinolone prescription fills in the United States, August 2014 through February 2020. From August 2014 through May 2016 (baseline period), there were no significant changes in monthly prescription fills per 1,000 persons (*y* axes) of ciprofloxacin, levofloxacin, and total fluoroquinolones; there was a significant decrease in monthly moxifloxacin fills ($P = 0.009$). There were significant reductions in monthly prescription fills in May 2016 (indicated by first vertical dashed line) of ciprofloxacin ($P = 0.001$), levofloxacin ($P = 0.006$), moxifloxacin ($P = 0.04$), and total fluoroquinolones ($P < 0.001$). Throughout the first warning period (May 2016 to June 2018), there was a significant decrease in monthly prescription fills of total fluoroquinolones ($P < 0.001$), ciprofloxacin ($P < 0.001$), and moxifloxacin ($P = 0.001$); there was no change in prescription fills of levofloxacin. Prescription fill trends during the first warning period of total fluoroquinolones ($P = 0.02$) and ciprofloxacin ($P = 0.001$) were significantly greater than corresponding trends during the baseline period; there was no change in the trend of prescription fills of levofloxacin and moxifloxacin. There were no significant changes in monthly prescription fills in July 2018 (indicated by second vertical dashed line) of total fluoroquinolones, ciprofloxacin, levofloxacin, and moxifloxacin. Throughout the second warning period (July 2018 to February 2020), there was a significant decrease in prescription fills of total fluoroquinolones ($P = 0.001$) and ciprofloxacin ($P < 0.001$), but this trend did not significantly differ from the trend during the first warning period. There was no change in monthly prescription fills of levofloxacin and moxifloxacin during the second warning period, and trends did not differ from corresponding trends during the first warning period. Note that scale on the *y* axis differs by agent. Monthly prescription fill data are presented as filled black circles. Predicted trends of prescription fills of each antibiotic are presented as solid black lines.

during the baseline period and decreased significantly in the first month of the first warning period (May 2016). In contrast to trends for ciprofloxacin and fluoroquinolones overall, reductions in levofloxacin fills during the first warning period (May 2016 to June 2018) were not significant. Likewise, there were no significant decreases in levofloxacin fills during the first month of the second warning period (July 2018) or throughout that period (July 2018 to February 2020). Trends in monthly prescription fills of levofloxacin did not significantly differ during baseline or first warning or second warning periods.

Monthly moxifloxacin fills decreased significantly throughout the baseline period, during the first month of the first warning period, and throughout the first warning period. Trends of moxifloxacin fills were similar to one another in baseline and first warning periods. Prescription fills did not change in the first month of the second warning period or throughout that period. Monthly prescription fills of moxifloxacin plateaued

during the second warning period, with a significant change in the trend line compared to baseline or first warning periods.

There was no significant change in amoxicillin prescription fills during the baseline, first warning, or second warning periods. There was no significant change in amoxicillin prescription fills during the first month of the first warning period or the first month of the second warning period (Table 3; Fig. 1).

Fluoroquinolone prescriptions by clinicians from various specialties. The percentages of fluoroquinolone prescription fills written by clinicians from various specialties over the 5-year study period were as follows: internal medicine (20.8%), family medicine/general practice (16.6%), nurse practitioners (11.5%), osteopathic medicine (10.4%), physician assistants (8.9%), urologists (6.4%), and emergency medicine (5.3%). Other specialties were each responsible for <5% of fluoroquinolone prescription fills. Significantly more prescriptions were filled annually for fluoroquinolones ordered by nurse practitioners and infectious diseases specialists from 2015 through 2019 (Table 2). There was no change during this period in fluoroquinolone prescription fills written by physician assistants, dentists, and nephrologists (Table 2). For other clinician specialties, prescription fills of total fluoroquinolones significantly decreased annually (Table 2).

DISCUSSION

To our knowledge, this is the first study to report on recent trends of outpatient fluoroquinolone prescription fills in the United States and on the impact of FDA safety warnings on these patterns. Three findings are particularly notable. First, there were significant annual reductions in fills of fluoroquinolones as a class from 2015 through 2019 and in fills of ciprofloxacin, levofloxacin, and moxifloxacin as individual agents. Fluoroquinolone prescription fills decreased by 42% during the study period, which equated to approximately 47 fewer fills per 1,000 persons per year. Ciprofloxacin, levofloxacin, and moxifloxacin fills decreased by 39%, 43%, and 65%, respectively. Second, reductions in fluoroquinolone fills were temporally associated with the May 2016 FDA safety warning. Prior to this announcement, monthly reductions in fluoroquinolone fills from August 2014 through April 2016 were not significant. However, fills dropped significantly in May 2016, and they continued to decrease significantly through June 2018 (the first warning period). The July 2018 FDA warning did not significantly impact prescription fills, and the subsequent monthly trend in decreasing fills was similar to that observed for the first warning period. Third, as overall fluoroquinolone use dropped, fills of prescriptions from infectious diseases specialists and, to a lesser extent, nurse practitioners, increased. Taken together, our data demonstrate national progress toward achieving stewardship goals for outpatient fluoroquinolones and attest to the impact of FDA safety warnings in limiting the use of these drugs.

Outpatient agents account for over 80% of total antibiotic prescribing in the United States (CDC), but antimicrobial stewardship endeavors in these settings have lagged behind those of inpatient stewardship. It is notable that the CDC published *Core Elements of Outpatient Antibiotic Stewardship*, a national call to arms for improved practices, in November 2016, shortly after the FDA's May 2016 safety warning for fluoroquinolones (4; https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-advises-restricting-fluoroquinolone-antibiotic-use-certain). The reduction in outpatient fluoroquinolone use in May 2016 suggests that the warning immediately impacted clinicians' prescribing habits. It is also likely that ongoing reductions in outpatient fluoroquinolone prescription fills through February 2020 stemmed, at least in part, from stewardship efforts that leveraged FDA warnings and safety data. Moreover, the impact of these efforts appeared specific to reducing fluoroquinolone prescribing. Fills of amoxicillin, the most commonly prescribed outpatient antibiotic in the United States at the start of the study period (12), were not affected by fluoroquinolone FDA warnings and did not change significantly from 2015 through 2019. Likewise, reductions in fluoroquinolone use could not be ascribed to significant increases in resistance rates.

According to the SENTRY database, 30.1%, 30.6%, 30.2%, 29.2%, and 27.1% of *Escherichia coli* isolates from U.S. medical centers were resistant to ciprofloxacin in 2015, 2016, 2017, 2018, and 2019, respectively (13). In individual U.S. health care systems, multifaceted stewardship strategies that included safety warnings have been effective in reducing overall and inappropriate fluoroquinolone prescriptions in some instances, although sustained benefit often depends upon ongoing interventions (5–8).

Prior to 2016, FDA issued warnings about fluoroquinolones in July 2008, March 2011, and August 2013 (Table 1) (https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics-risks-mental-health-and-low-blood-sugar-adverse). Previously published national prescription data do not suggest that these warnings had a significant impact on reducing fluoroquinolone use (1). The seeming impact of the May 2016 warning may reflect enhanced awareness of outpatient antimicrobial stewardship, ADEs, and patient safety issues in general. The May 2016 warning was the most explicit and far-reaching of those released by the FDA, advising that serious ADEs associated with fluoroquinolone use generally outweighed benefits for patients with common conditions like acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections (UTIs). Acute sinusitis is the most frequent diagnosis leading to an antibiotic prescription in the United States, and acute bronchitis and UTIs are among the top 7 indications (14). The warning also specifically referred to "disabling and potentially permanent adverse events" involving tendons, muscles, joints, nerves, and the central nervous system. FDA communications in 2018 more narrowly strengthened warnings about ADEs involving changes in blood glucose levels and mental health, and they added a warning about rare aortic complications. While the 2018 warnings did not demonstrably improve downward trends in fluoroquinolone prescription fills, it is plausible that they helped maintain the favorable trajectory.

Changing patterns of fluoroquinolone fills were driven most strongly by use of ciprofloxacin, the most commonly prescribed agent within the class. As for fluoroquinolones overall, monthly ciprofloxacin fills did not decline significantly during the baseline period (August 2014 through April 2016) but did decrease significantly in May 2016 and throughout the first warning period (May 2016 through June 2018). The downward trend in ciprofloxacin fills was maintained (but not enhanced further) in July 2018 and monthly during the second warning period (through February 2020). The most significant reduction in levofloxacin fills was in May 2016, but trends during the first warning period did not significantly differ from those of the baseline period. In contrast, moxifloxacin fills decreased significantly throughout the baseline period, in May 2016, and throughout the first warning period. Despite the slight differences in the association between FDA warnings and use of particular agents, prescription fills of ciprofloxacin, levofloxacin, and moxifloxacin decreased annually by 10.4%, 11.2%, and 17.7%, respectively, from 2015 through 2019. Each of the drugs was available as a generic formulation during the study period.

Annual fills of fluoroquinolones prescribed by most types of clinician specialty decreased significantly, including those ordered by the two largest groups (internists and family medicine/general practitioners, who accounted for almost 40% of prescriptions). The only specialties for which prescriptions fills were significantly increased were infectious diseases specialists and nurse practitioners. The reasons for increased prescribing by these groups are unclear but merit further investigation. It is plausible that as concern about fluoroquinolone safety increased and prescribing by other specialties decreased, more patients who needed one of these agents were seen by infectious diseases specialists. Infectious disease specialists may be more likely than others to prescribe oral antibiotics with relatively high bioavailability, such as fluoroquinolones, in lieu of intravenous agents for diseases like bone and joint infections and infective endocarditis (15, 16). It is also possible that stewardship programs have increasingly mandated that fluoroquinolone prescriptions be approved or ordered by infectious diseases specialists. Increased fluoroquinolone prescribing by nurse

practitioners may reflect the more prominent role they now play in the U.S. health care system. Indeed, the number of licensed nurse practitioners doubled from 2007 to 2018 (https://www.aanp.org/news-feed/nurse-practitioner-role-continues-to-grow-to-meet-primary-care-provider-shortages-and-patient-demands).

There are several limitations to our study. We only included data on the three most commonly prescribed fluoroquinolones. Nevertheless, ciprofloxacin, levofloxacin, and moxifloxacin account for the overwhelming majority of fluoroquinolone prescriptions in the United States. Information on indications, quantify, durations, dosages, and appropriateness of prescriptions are lacking in IQVIA NPA databases, as are patient- and provider-level data. As such, we cannot comment on overall volumes of fluoroquinolone consumption or on whether clinicians used agents more responsibly. Finally, it is important to reiterate that data are for prescription fills rather than written prescriptions.

In conclusion, fills of fluoroquinolone prescriptions by outpatient pharmacies in the United States decreased significantly over 5 years leading up to the onset of the coronavirus disease 2019 (COVID-19) pandemic. Decreases were associated with FDA safety warnings issued in 2016. Our findings suggest that FDA safety announcements can have a significant impact on drug use. Studies are warranted on other factors that may have contributed to decreased fluoroquinolone prescription fills, such as antimicrobial stewardship practices, evolving national resistance patterns, and use of alternative agents. This study supports the use of FDA safety announcements as powerful tools to increase prescriber awareness of ADEs and to leverage antimicrobial stewardship initiatives.

MATERIALS AND METHODS

Study population and data sources. We obtained pharmacy fill data for the three most commonly prescribed fluoroquinolone antibiotics (ciprofloxacin, levofloxacin, and moxifloxacin) in the United States from IQVIA NPA databases (Durham, NC) for August 2014 through February 2020. February 2020 was chosen as the end date to avoid the impact of the coronavirus disease 2019 (COVID-19) pandemic on antibiotic prescribing (12). We also obtained pharmacy fill data for amoxicillin from IQVIA NPA databases to serve as a control antibiotic that was not the subject of FDA warnings during the study period. NPA databases provide national monthly estimates of prescriptions dispensed from retail pharmacies (chain, mass merchandiser, independent, and food store) to patients. Prescription fill data are obtained from 92% of retail pharmacies, and they are projected to approximate 100% of all dispensing in the United States. Data were provided as numbers of prescriptions filled monthly for formulations of ciprofloxacin, levofloxacin, moxifloxacin, and amoxicillin. A prescription for any quantity of any dose of any agent was counted as 1 prescription (e.g., prescriptions filled for 10 ciprofloxacin 500 mg tablets and 20 ciprofloxacin 500 mg tablets were each counted as 1 prescription). We included prescriptions for any tablet, capsule, or oral suspension formulation of these agents. Clinician specialty associated with each fluoroquinolone prescription was obtained and aggregated. Clinician specialties included the following: family and general practice, internal medicine, nurse practitioner, osteopathic medicine, physician assistant, urology, emergency medicine, obstetrics and gynecology, general surgery, geriatrics, oncology, otolaryngology, pediatrics, podiatry, dentistry, nephrology, internal medicine/pediatrics, infectious diseases, unspecified specialties, other medical subspecialty, other surgical subspecialty, and other. Prescription rates per 1,000 persons were calculated using U.S. Census estimates of the monthly national population (https://www.census.gov/data/tables/time-series/demo/popest/2010s-national-detail.html).

Interventions and outcomes. The study was designed to assess FDA warnings in 2016 and 2018 (Table 1). In May 2016, an FDA drug safety communication advised that serious ADEs outweighed the benefits of fluoroquinolones for patients with certain uncomplicated infections (acute sinusitis, acute bronchitis, and urinary tract infections [UTIs]), and these agents should be reserved for patients in whom alternative treatment options were not available (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-advises-restricting-fluoroquinolone-antibiotic-use-certain). The FDA revised the existing boxed warning to include this language in July 2016 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics). Further warnings were added to labeling in July 2018 about risks for significant hypoglycemia and mental health side effects (https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side). Five months later, a drug safety communication warned of the risk for aortic dissection and aortic aneurysm rupture (https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics).

We defined August 2014 through April 2016 as the baseline period. The FDA warning issued in May 2016 was the first warning, and May 2016 through June 2018 was defined as the first warning period. The warning issued in July 2018 was the second warning, and July 2018 through February 2020 was defined as the second warning period.

The primary outcome of the study was monthly outpatient prescriptions of ciprofloxacin,

levofloxacin, and moxifloxacin filled by retail pharmacies in the United States per 1,000 persons. Secondary outcomes were monthly outpatient ciprofloxacin, levofloxacin, and moxifloxacin prescriptions by clinician specialty per 1,000 persons.

Statistical analysis. We analyzed yearly data from 2015 through 2019 using a regression model to evaluate change in prescription fills of fluoroquinolones per year. An interrupted time series regression model (segmented regression, Newey-West standard errors) was used to estimate changes in monthly prescription fills that occurred after the FDA issued safety warnings. Regression coefficients were estimated by ordinary least squares and controlled for previous trends and autocorrelation (seasonal effects). *P* values of <0.05 were considered significant. Data were analyzed using STATA 16.1 (StataCorp LLC, College Station, TX).

ACKNOWLEDGMENTS

We thank Alan Carr for assistance in compiling and interpreting IQVIA NPA data.

C.J.C. has been awarded investigator-initiated research grants from Astellas, Merck, Melinta, and Cidara for studies unrelated to this project; served on advisory boards or consulted for Astellas, Merck, the Medicines Company, Cidara, Scynexis, Shionogi, Qpex and Needham & Company; and has spoken at symposia sponsored by Merck and T2Biosystems. D.J.B. served on advisory boards for Shionogi.

There was no funding for this study.

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